R E M A R K S

The Office Action mailed June 20, 2001 has been reviewed. Favorable reconsideration is respectfully requested in view of the preceding amendments and the following comments.

Other than the editorial corrections to claims, antecedent support for the weight limitation is provided by the sentence bridging pages 2 and 3 of the specification.

The rejection of claims 25 and 29 "under 35 U.S.C. 112, second paragraph" is respectfully traversed. The alleged indefiniteness of claim 25 has been overcome by deleting "26." from line 3 of that claim.

The weight ratio of mizolastine was questioned. As the employed terminology is that which is commonly used by those of at least ordinary skill in the art, any artisan would understand the intended meaning to be that the ratio is from 3 parts by weight of mizolastine to 10 parts by weight of the organic acid to a 1/1 weight ratio of mizolastine to the organic acid.

The issue with regard to claim 29 is not understood. Page 3 of the specification (line 14) specifically points out that L-tartaric acid is the particularly preferred organic acid.

Applicants note that no ground of rejection has been applied to claim 23. It is thus understood that this claim is presently in condition for allowance, and confirmation of that point is respectfully solicited.

In response to the prior Office Action mailed October 11, 2000, Applicants provided a fairly detailed review of requirements for combining references, none of which have been addressed in Paper No. 8. For a viable rejection based on a combination of references, the cited authorities must be complied with. Applicants respectfully submit that the rejections based on a combination of references fail to satisfy the requirements pointed out in Applicants' prior response.

The rejection of claims 21, 22, 24 to 26, 30 to 34, 38 and 39 "under 35 U.S.C. 103(a) as being unpatentable over US 4,590,062 ('062) in combination with the HCAPLUS abstract of Desager et al. ..." is respectfully traversed. When facing the problem of overcoming the undesirable sedative effects of mizolastine, nothing is found in either reference that would lead any artisan to combine their teachings to solve the problem faced and solved by Applicants' claimed invention. The selection of references is thus one which is predicated solely on Applicants' own teachings, rather than anything garnered from the applied art itself. It is clear that there is nothing in either of these references that would even remotely suggest either the solution to Applicants' problem or that the subject matter called for by the involved claims would be successful in overcoming that problem.

In addition, each of the claims is now limited to a dosage form wherein the mizolastine comprises from 0.5% to 12% by

weight of the dosage form. In order to evaluate the lack of prior-art teaching with regard to Applicants' claimed invention, it is necessary to consider the teachings away from the claimed invention as well as those alleged to render it "obvious".

In this connection reference is respectfully made to the teachings of Khan (USP 5,656,296)• wherein control sustained release coated tablets for antihistamines are contemplated. In the exemplary formulations set forth in Table 1, the formulations comprise from 79 to 81% of active ingredient. This is a far cry from the 0.5% to 12% by weight, to which each of the rejected claims is limited. No suggestion is found in any applied art of mizolastine sustained-release coated tablets having that small a percentage of active component.

The rejection of claims 21, 22, 24 to 26, 30 to 34, 38 and 39 "under 35 U.S.C. 103(a) as being unpatentable over US 5,656,296 ('296) in combination with Desager et al." is also respectfully traversed in the same manner and for the same reasons as set forth in the preceding remarks. Khan is actually a clear teaching away from the subject matter called for by each of these claims, as previously explained. In the light of Khan's teachings there is clearly no reason to believe that the formulations called for by Applicants' claims would even be effective.

Issue is respectfully taken with the allegation that Desager et al. "teach that mizolastine is an effective

antihistamine that does not cause drowsiness." What Desager actually states is:

> This review is mainly devoted to second generation antihistamines that possess a low sedation potential compared with first generation compds.

Thus, all that is stated in the provided abstract is that the enumerated antihistamines "possess a low sedation potential compared with first generation compounds"; it does not relate to any fashion of reducing the sedation effect of mizolastine.

Kahn repeatedly points out that the core of his coated tablets comprises from about 60% to about 90% medicament. Reference is respectfully made to the formulations presented on page 4 and 5 of Applicants' specification to appreciate the significant difference in the compositions that are presently called for by the involved claims.

Issue is respectfully taken with the unsupportable allegation that the "prior art composition contains the same components and would inherently exhibit the same properties"; such must be recognized as a non sequitur in view of the vast difference in amounts of active ingredients involved.

Once more, there is no suggestion in either of these references that the undesirable sedative effects of mizolastine would be reduced or eliminated by Applicants' claimed subject matter. When the art teaches a proportion of from 60 to 90% by weight of medicament, it must be regarded as completely non-obvious

to have proportions as low as those expressly called for by Applicants' claims and also find that the adverse sedative effect is significantly reduced or even eliminated.

The rejection of claims 27 to 29, 35 to 37 and 39 to 43 "under 35 U.S.C. 103(a) as being unpatentable over US 4,590,062 ('062) in combination with Desager et al. ... and further in view of US 5,102,666 ('666)" is also respectfully traversed in the same manner and for the same reasons as set forth in the preceding remarks. Applicants respectfully submit that Acharya ('666) has absolutely nothing to do with Applicants' claimed invention. The selection of this reference must be regarded as entirely based on Applicants' own teachings, as it has nothing to do with the problem faced and solved by Applicants.

Acharya essentially concerns a formulation for controlled release of an active composition "especially useful for local, parenteral, buccal, gingival, and oral controlled release of active compositions" (column 1, lines 10 to 12) "used to contact an area of skin or mucous membrane to be treated with said active composition" (column 3, lines 21 to 23). Acharya "provides a method of control release treatment through use of a polymeric carrier and a therapeutically effective amount of an active composition which is a 'complex hydrogel' that is formed within the body after it is administered, to provide control release of an active agent from the matrix over the course of a few days to a few

months." (Column 3, third complete paragraph). Both the compositions and their intended use and mode of operation are entirely unrelated to Applicants' claimed subject matter.

The method of treatment contemplated by Acharya is described in the paragraph bridging columns 11 and 12 and the first complete paragraph of column 12. Such method of treatment is evidence of the complete incompatibility of teachings of this reference with the subject matter to which Applicants' claims are directed.

Please note, as well, that Acharya refers to tartaric acid in the enumeration of "breath fresheners and flavors"; it is most unlikely that one skilled in the art would add a flavoring or a breath freshening agent to a formulation to be swallowed and which does not stay in the mouth. It is truly unlikely that a component which has no reason to be included in the formulation would be considered by anyone of at least ordinary skill in the art. Acharya's reference to tartaric acid (in context) is completely irrelevant to Applicants' claimed invention.

The rejection of claims 27 to 29, 35 to 37 and 39 to 43 "under 35 U.S.C. 103(a) as being unpatentable over US 5,656,296 ('296) in combination with Desager et al. ... and further in view of US 5,102,666 ('666)" is also respectfully traversed in the same manner and for the same reasons as set forth in the preceding remarks with regard to each of the respective references. The

allegation "that tartaric acid can be added to controlled release tablets containing antihistamines for flavoring and breath freshening" is regarded as rather farfetched when applied to a tablet which is promptly swallowed, rather than retained in the oral cavity.

Issue is respectfully taken with the unsupported allegation that "US '666 encompasses both a racemic mixture and any individual isomers of tartaric acid." If this position is maintained, the Examiner is respectfully requested to point out precisely the text of '666 which supports such conjecture.

As pointed out in the second complete paragraph on page 6 of the specification, "the bioavailability of the formulation containing no L-tartaric acid represents only 43% of that observed with the formulation according to the invention containing L-tartaric acid." The increase in bioavailability afforded by the presence of L-tartaric acid must be completely unexpected from any teaching of tartaric acid as a flavoring or breath freshening agent.

Having overcome all outstanding grounds of rejection, favorable action on the merits is now in order and is respectfully solicited. If the Examiner believes that an interview could advance the prosecution of this application, she is respectfully invited to telephone undersigned counsel.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "Version with markings to show changes made".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

21. (Amended) [Coated] A coated sustained release tablet, consisting essentially of from 0.5% to 12% by weight of mizolastine, a fatty matrix, an organic acid and a coating.

22. (Amended) [Coated] A coated sustained release tablet according to claim 21, [consisting essentially of mizolastine, a fatty matrix, an organic acid, and a coating, the coated tablet having] which has a dissolution profile which is pH independent.

23. (Amended) [Coated] A coated sustained release tablet, consisting essentially of mizolastine, a fatty matrix, an organic acid, and a coating, the coated tablet having a dissolution profile which is pH independent, the organic acid being a member selected from the group consisting of maleic, tartaric, malic, fumaric, lactic, citric, adipic and succinic acid in the form of a racemate or an isomer.

24. (Amended) A pharmaceutical dosage form which comprises a coated tablet having a sustained-release core, said core comprising a combination of:

a) mizolastine as active principle;

b) a fatty matrix; and

c) an organic acid;

and wherein the mizolastine comprises from 0.5% to 12% by weight of the dosage form.

25. (Amended) A sustained-release pharmaceutical dosage form according to claim 24 wherein the weight ratio [between] of the mizolastine [and] to the organic acid is between 0.3 and 1. [26.]

31. (Amended) A coated sustained-release tablet having:

a) a core comprising mizolastine, a fatty matrix and an organic acid; [and]

b) a dissolution profile which is pH independent; and

c) wherein the mizolastine comprises from 0.5% to 12% by weight of the tablet.